"burning pain") and discussed various treatment methods. As recently as 1965, the American Academy of Neurology reprinted *Injuries of Nerves and Their Consequences*, referring to Mitchell as the "father of American neurology."

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More about hyperprolactinemia

In the comprehensive review of hyperprolactinemia by Omar Serri and associates[1] the answers to some important questions remain unclear.

Fig. 2 of the article recommends MRI of the pituitary if pathologic hyperprolactinemia is identified on repeat measurement of prolactin, but there is no definition of what constitutes pathologic hyperprolactinemia. It appears that the authors are suggesting MRI of the pituitary if the prolactin level remains elevated on repeat measurement, but what extent of elevation should lead to consideration of MRI? For example, should the physician perform imaging studies if the prolactin level is marginally elevated but still less than 100 μg/L? In clinical practice, patients with marginally elevated levels on 2 or 3 occasions often undergo imaging studies of the pituitary gland, but is this practice justified? Consideration of MRI of the pituitary is one of the most important clinical decision-making points in the management of hyperprolactinemia, so it would be helpful to have some guidance in this regard.

In addition, to what extent does nipple or breast stimulation cause elevation in prolactin levels, and how long should the patient avoid such stimulation before the repeat measurement of prolactin is performed?

Turning to the causes of this condition, Fig. 1 of the article lists anti-ulcer agents, specifically H_2 antagonists, as medications causing elevation of prolactin levels. However,[2] other medications, metoclopramide and domperidone[2] (motility agents commonly used in patients with gastroesophageal reflux), are dopamine antagonists and are more likely than H_2 antagonists to cause elevated prolactin levels. These drugs should be considered as causative agents and should be discontinued before further investigations are undertaken.

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The recent review by Omar Serri and associates[1] on the diagnosis and management of hyperprolactinemia did not address the important issue of a potential link between hyperprolactinemia and increased risk of breast cancer. This omission is not unique; in fact, no recent review on the management of hyperprolactinemia mentions the issue.[2,3] However, concern about such an association is often raised by psychiatrists and their patients because hyperprolactinemia can be caused by certain atypical antipsychotic medications and selective serotonin release inhibitors.[4] A recent comprehensive review[5] reported that laboratory studies have shown definitively that prolactin stimulates both normal and cancerous breast tissue to grow and differentiate in culture. However, in the clinical setting there are too few data to allow conclusions either way. The sole large prospective trial cited in the review[5] did establish an association between hyperprolactinemia and increased risk of breast cancer among postmenopausal (but not premenopausal) women. Other epidemiological evidence reviewed by Clevenger and colleagues[5] suggested a strong link among breast cancer, oral contraceptive use and hyperprolactinemia.

There is a physiologic basis to explain why prolactin can stimulate breast cancer cells to grow and differentiate in culture but might not readily do so in vivo. When prolactin is elevated, the gonadotropins and sex steroids are normally suppressed. Thus, a potent and well-recognized stimulus for breast cancer growth (estradiol) is reduced at the same time that a likely weaker stimulus (prolactin) increases. This may explain why normal lactation (prolactin increased, estradiol reduced) has been associated with reduced risk of breast cancer in several studies.[6,7] Conversely, it may also explain the association, reported by Clevenger and colleagues,[5] between increased risk of breast cancer and the combination of oral contraceptive use and hyperprolactinemia (prolactin and synthetic estradiol-equivalent both increased).

The current standard of practice in the management of hyperprolactinemia is to leave asymptomatic patients untreated unless there is a lesion of the pituitary that needs control. However, many of my patients object to that approach because of uncertainty about whether hyperprolactinemia is truly benign to breast tissue, and many have opted for treatment of their asymptomatic hyperprolactinemia (or discontinuation of the causative medication).

We clearly lack the definitive data needed to reassure our patients about the long-term risks of hyperprolactinemia. Carefully controlled prospective studies are needed to determine the increase in risk of breast cancer (if any) for a woman with chronic hyperprolactinemia. In the meantime, it would be helpful if review articles on managing hyperprolactinemia addressed this issue. For example, algorithms for management (such as that on page 579 of the article by Serri and associates[1]

might include an arm for treatment of asymptomatic patients who are concerned about possible long-term risks.

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[Two of the authors respond:]

The causes of hyperprolactinemia fall into 3 main categories: physiologic, pharmacologic and pathologic. Pathologic hyperprolactinemia is due to hypothalamo-pituitary lesions and secondary causes such as hypothyroidism or renal or adrenal insufficiency. Clearly, any secondary causes must be ruled out before imaging of the pituitary is considered. We proposed MRI of the pituitary as the next logical step after repeat determination of prolactin levels and exclusion of physiologic, pharmacologic and secondary causes of hyperprolactinemia, regardless of the extent of elevation of prolactin.[1] Any specific cutoff value below which MRI would not be performed (such as 100 μg/L) might miss some nonlactotrophic hypothalamic or pituitary lesions that would present with slight to moderate hyperprolactinemia. The latter conditions require different management approaches from those for microprolactinomas.

Suckling in breast-feeding women is known to stimulate prolactin release. Moreover, breast stimulation in some non-breast-feeding normal women and rarely in some men may also cause an increase in serum prolactin levels.[2,3] Therefore, measurement of serum prolactin level should be avoided in the hours after breast stimulation or examination and ideally would be performed on another day.

We agree with Malvinder Parmar that metoclopramide and domperidone are potentially potent dopamine antagonists that can and frequently do result in significant hyperprolactinemia. Interruption or substitution of such agents, as indicated in our review,[1] should clarify their role in raising prolactin levels.

Christopher Kovacs raises a controversial issue that we did not address because of space limitations: the possible relation between increased prolactin levels and nonreproductive functions, including putative mitogenic and immune modulatory properties. Prolactin is a member of a family of growth factors that includes growth hormone, placental lactogen and placental growth hormone. These polypeptides can exert mitogenic effects in tissues expressing dedicated receptors. As indicated by experimental and animal models, mammary tissue expresses prolactin receptors and is positively influenced by prolactin.[4] However, prolactin is not a sufficient stimulus to cause malignant transformation. Furthermore, the data regarding the role of prolactin in human cancer have been conflicting. Some studies have suggested that higher circulating levels of prolactin are associated with an increased risk of radiographically dense breast tissue.[5] Others have noted that postsurgical hyperprolactinemia is associated with a significantly lower recurrence rate and longer disease-free and overall survival in node-negative breast cancer patients.[6] In addition, in patients with chronically elevated prolactin levels (such as those with prolactinomas) no increase in neoplasia in general or breast cancer in particular has been noted.[7] We do not feel that the weight of evidence regarding the relation between excess prolactin and the risk of neoplasia is sufficient to form the sole basis for recommending inhibition of prolactin for postmenopausal women.

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